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Regulation of hematopoiesis by the chemokine system

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ABSTRACT

Although chemokines are best known for their role in directing cell migration, accumulating evidence indicate their involvement in many other processes. This review focus on the role of chemokines in hematopoiesis with an emphasis on myelopoiesis. Indeed, many chemokine family members are an important component of the cytokine network present in the bone marrow that controls proliferation, retention, and mobilization of hematopoietic progenitors.

1. The chemokine system

Chemokines are a large family of chemotactic cytokines consisting of more than 50 molecules. The name “chemo-kines” derives from their capacity to cause chemotaxis in responsive cells, which express related chemokine receptors. Chemokines have low amino acid sequence homology, but they all have a conserved tertiary structure, consisting of a disordered amino-terminus, three-stranded antiparallel β-sheet and a carboxy-terminal α-helix [2].

Depending on the position of the cysteine residues in their N-terminus, chemokines are divided in four subfamilies: CC, CXC, C and CX_3C [54,19]. The chemokine subfamilies CC, CXC and CX_3C have four well-conserved cysteine residues, which form two disulphide bonds between the first and the third cysteine and between the second and the fourth cysteine. The CC chemokines are the largest subfamily of chemokines and have the first two of the four cysteine residues in adjacent position, while the CXC and CX_3C chemokines have one and three amino acids separating the two cysteines, respectively. The CXC chemokines can be further subdivided in ERL− and ERL+ chemokines, based on the presence or absence of the ELR (Glu-Leu-Arg) motif [40]. In general, ERL− chemokines exhibit an anti-angiogenic activity, whereas ERL+ chemokines are angiogenic factors [60,61]. Finally, the XC subfamily is composed by only two chemokines having only two cysteines in their sequence.

Based on their expression pattern, chemokines can be also classified as homeostatic or inflammatory ones [34]. Homeostatic chemokines (e.g. CXCL12, CXCL13, CCL14, CCL19) are constitutively produced and regulate basal leukocyte trafficking, such us lymphocyte homing to secondary lymphoid organs. Inflammatory chemokines (e.g. CCL2, CCL5, CXCL8) are inducible molecules secreted during inflammatory responses, upon infection or tissue injury and they drive leukocyte recruitment to the site of inflammation.

The specific function of each chemokine is determined by the expression of chemokine receptors on target cells [5].Chemokine receptors are 7-transmembrane (7TM) receptors coupled to hetero-trimeric GTP-binding proteins (G-protein) of the Gi type, sensitive to Bordetella pertussis toxin. Depending on the chemokines they bind, chemokine receptors are classified as CXCR, CCR, CX_3CR, or XCR and can be either inflammatory or homeostatic [47].

Beyond canonical chemokine receptors, a smaller family of atypical chemokine receptors (ACKRs) has been identified [4]. ACKRs share many similarities with canonical chemokine receptors and bind ligands with high affinity but show structural modifications in the motif that is essential for G-protein interaction. As result, ACKRs are unable to couple to G protein and to promote cell migration [8], and they act as scavengers, transporters or depots for the chemokines they bind. The family of ACKRs includes four receptors named ACKR1 (previously called DARC), ACKR2 (D6), ACKR3 (CXCR7), and ACKR4 (CCX-CKR) [4].

Most studies on chemokines and chemokine receptors were focused on their ability to chemoattract leukocytes. However, it is known from several years that chemokines regulate additional functions in leukocytes. For instance, CXCR2 ligands regulate effector functions of neutrophils [6] and CCL19, acting on CCR7 expressed by dendritic cells,

Abbreviations: HSCs, hematopoietic stem cells; CMPs, common myeloid progenitors; GMPs, granulocytes-macrophages progenitors; ACKRs, atypical chemokine receptors; MEPs, megakaryocyte-erythrocyte progenitors; HPCs, hematopoietic progenitor cells; NECs, nucleated erytrocyte precursors

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regulates their survival [55]. Here, we resume data on the role of chemokines in the control of differentiation, mobilization, and proliferation of hematopoietic progenitors.

2. Hematopoiesis

Hematopoiesis is a dynamic process by which hematopoietic stem cells (HSCs) proliferate and differentiate into mature blood cellular components. HSCs are a rare population of cells characterized by an extensive self-renewal capability and pluripotency. The division of HSCs can result in the production of additional HSCs or hematopoietic progenitor cells (HPCs), that have a limited self-renewal capability and consist of cells in which multipotency is restricted [33,1,32].

In adult life, hematopoiesis takes place into the bone marrow (BM) whereas during fetal development, since BM is not yet developed, liver, thymus and spleen may assume hematopoietic function [7].

Histological analysis revealed that during adulthood, HSCs are mainly located in restricted areas of BM, called as BM HSC niches consisting of both hematopoietic and non-hematopoietic cell types. In particular, HSCs are associated with cells of mesenchymal origin, sinusoidal endothelium, and with arterioles [20]. HSC niche represents a complex microenvironment that provides the signals necessary to maintain physiological homeostasis and to achieve the balance between HSC renewal and differentiation. These signals can enhance or suppress the growth, survival and movement of HSCs and progenitor cells. Adhesion molecules such us P-selectin, E-selectin and vascular cell adhesion molecules (VCAM-1) are expressed by niche stromal cells and control HSC maintenance and function by the interaction with their specific receptors on HSCs [41]. On the other hand, the niche elaborates also many cytokines and growth factors, such as stem cell factor (SCF), interleukin-3 (IL-3), interleukin-6 (IL-6) and colony-stimulating factors (CSFs), that are essential for the initial rounds of cell division and differentiation of HSCs [46]. As we will discuss below, an important player in the interaction between HSCs and the niche is the CXCR4/CXCL12 axis [63].

3. Myelopoiesis

Myelopoiesis specifically refers to the process that leads to myeloid cell production [7]. Myeloid cells derive from HSC differentiation into common myeloid progenitors (CMPs) that are cells committed to the myeloid lineage, and give rise to granulocyte-macrophage progenitors (GMPs) and megakaryocyte-erythrocyte progenitors (MEPs). Next, the differentiation of GMPs and MEPs gives rise to whole lineage of myeloid cells, including monocytes, macrophages, granulocytes, platelets, erythrocytes, and dendritic cells (DCs) [33,1,32]. It has been demonstrated in mice that tissue resident macrophages in liver (Kupffer cells), spleen (red pulp macrophages), brain (microglia), epidermis (Langerhans cells), lung (alveolar macrophages), peritoneum (large peritoneal macrophages), pancreas, kidney and heart (F4/80^{bright} macrophages) originate from precursor cells in the yolk sac. They are long-lived and can proliferate within their tissue of residence [35,66]. However, with the exception of microglia, tissue resident macrophages are progressively replaced by BM-derived progenitors throughout the lifespan of the animal [52].

The cytokines of the colony stimulating factor (CSF) family are the major orchestrators of myelopoiesis; they were defined by their abilities to generate in vitro colonies of mature myeloid cells from BM precursor cells, and they include: macrophage CSF (M-CSF; also known as CSF1), which supports macrophage differentiation; granulocyte-macrophage colony stimulating factor (GM-CSF; also known as CSF2), that stimulate the proliferation and differentiation into monocytes and DCs; and granulocyte colony stimulating factor (G-CSF; also known as CSF3), which is important for the differentiation of neutrophil progenitors and precursors [46]. However, within the microenvironment where HPCs reside, they are likely influenced by a huge number of other cytokines, including chemokines.

4. Chemokines in hematopoiesis

The role of chemokines and their receptors in hematopoiesis encompasses the regulation of proliferation as well as the survival and the retention of hematopoietic progenitors. In particular the CXCL12-CXCR4 axis is fundamental for HSC homeostasis [30] and at least 24 chemokines belonging to CC, CXC and C families have been reported to be endowed with myelosuppressive activity in vivo e in vitro [17,28,37,14,67,10,11].

In this review, we seek to resume data on the main chemokines and chemokine receptors that have been found involved in the regulation of homeostatic hematopoiesis.

4.1. CXCL12-CXCR4 axis

The chemokine CXCL12, also known as stromal derived factor-1 (SDF-1), is a representative homeostatic chemokine and it is expressed constitutively in the BM. CXCL12 is produced by a wide variety of cells in the niche, including perivascular mesenchymal stromal cells (MSCs), endothelial cells, osteoblasts, some hematopoietic cells, and by adipogenic progenitor cells with reticular shape [65,44]. The last cell type, given its profuse production of CXCL12, is named CXCL12-abundant reticular (CAR) cells and they are in close contact with HSCs. The production of CXCL12 by these cells is fundamental for the homeostasis of the hematopoietic niche [9]. Indeed, the binding of CXCL12 to the receptor CXCR4, expressed on HSCs, induces their retention in the BM. The relevance of the CXL12-CXCR4 axis is demonstrated by the fact that the CXCR4 antagonist AMD3100 (Plerixafor) is an approved drug for the mobilization of HSCs [22]. Moreover, the retention signal induced by the CXCL12-CXCR4 axis is also the target of proteolytic enzymes, such as Elastase, Cathepsin-G and CD26 that are known to induce HSC mobilization. Indeed, it has been demonstrated that these enzymes exert their mobilization activity by cleaving the N-terminal sequence of CXCL12. These NH_2-cleaved versions of CXCL12 are characterized by decreased activity or even an antagonistic effect to the uncleaved chemokine [46]. Interestingly, it was found that also G-CSF exerts its HSC mobilization effect through neutrophil activation and release of proteases, including MMP-9, that results in enhanced cleavage of c-kit, CXCL12, CXCR4, VCAM-1 and its receptor Very Late Antigen-4 (VLA-4) [62]. However, CXCL12 provides a retention signal for many other cells expressing CXCR4 in the BM, including committed progenitors and neutrophils [25].

In addition to control HSC retention in the BM, CXCL12 by interacting with CXCR4, has other important effects on hematopoiesis and myelopoiesis. This crucial role is corroborated by significant phenotypic changes in the hematopoietic system of mice lacking *Cxcl12* or *Cxcr4* genes. These mice, that have a late gestation lethal phenotype due to defective cardiac septum formation, have also defects in B-cell lymphopoiesis and virtually absent BM myelopoiesis [39,31]. In addition, the deletion of one copy of CXCR4 is sufficient to give a selective advantage for BM engraftment of HSCs. Indeed, *Cxcr4* haploinsufficiency enhanced HSC proliferation while maintaining long-term hematopoiesis [43]. Furthermore, CXCL12 regulates HSC mitochondrial respiration that is essential to maintain their undifferentiated state [45]. These observations indicate that CXCL12, beside its role in BM retention, has a role in keeping HSC quiescence, and maintaining a constant pool of HSCs to sustain hematopoiesis.

Behind its direct effect on HSCs, CXCL12 can also indirectly have impact on hematopoiesis. Studies in CXCR4-deficient mice have shown that the CXCL12–CXCR4 axis, by regulating the development of vasculature, can have a crucial effect on the stucture of the hematopoietic niche near the sinusoids [64].